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NIDN-10428

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	O. Axelsson, et al.	Group Art Unit:	To be assigned
Serial Number:	09/990,537	Examiner:	To be assigned
Filing Date:	November 16, 2001		
Title:	Process for Preparation of MR Contrast Agents		

Completion of Claim for Priority

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby submit the official certified copy of the priority document number **GB 9911681.6** in connection with the above identified application, benefit of which is claimed in the declaration of this application. The Examiner is most respectfully requested to acknowledge receipt of this certified copy in the next Official Office Action.

Respectfully submitted,

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The Patent Office
Cardiff Road
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1. **Your reference** 44.43.70219/000

2. **Patent application number** *(The Patent Office will fill in this part)* 19 MAY 1999 **9911681.6**

3. **Full name, address and postcode of the or of each applicant** *(underline all surnames)*
Nycomed Imaging AS
PO Box 4220
N-0401 Oslo
Norway

Patents ADP number *(if you know it)* 73738890001 Ades

If the applicant is a corporate body, give country/state of incorporation Norway

THE PATENT OFFICE
L
19 MAY 1999
LONDON

4. **Title of the invention** Process

5. **Name of your agent** *(if you have one)* Frank B. Dehn & Co. Catriona Macleod Hamnett Anthony John Rowe Audrey Gale Campbell

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
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Amersham plc
The Grove Centre
White Lion Road
Amersham
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Patents ADP number *(if you know it)* 166001

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11. **I/We request the grant of a patent on the basis of this application.**

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12. **Name and daytime telephone number of person to contact in the United Kingdom**

Julian Cockbain
0171 206 0600

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70219.604

Process

This invention relates to a process and apparatus for hydrogen-induced nuclear spin polarization of an unsaturated compound, and more preferably for the preparation of a contrast agent for a magnetic resonance imaging procedure.

Hydrogen molecules ($^1H_2$) exist in the different forms, namely para-hydrogen where the nuclear spins are anti-parallel and out-of-phase (the singlet state) and ortho-hydrogen where they are parallel or anti-parallel and in-phase (the triplet state). At room temperature, the two forms are in equilibrium with an approximately 1:3 ratio of para to ortho hydrogen. At 80K the ratio is about 48:52 and at 20K it approaches 100:0 (actually about 99.8:0.2).

In contrast, deuterium (D_2 or $^2H_2$), where the ^2H nucleus has a nuclear spin (S) of 1 rather than ½, exists in nine different forms, three anti-symmetric para forms and six symmetric ortho forms. At ambient temperature, the ratio of ortho-deuterium (o-D_2) to para-deuterium (p-D_2) in an ortho-/para-deuterium mixture is about 2:1, at 60K it is about 3:1 and at 20K it is about 98:2. (Deuterium freezes at about 19K).

In PCT/GB98/03399, a copy of which is filed herewith and the enclosures of which are hereby incorporated by reference, it is described how para-hydrogen may be used to catalytically hydrogenate unsaturated compounds, transferring to those compounds the anti-parallel proton spins of the para-hydrogen molecule, and transferring nuclear spin polarization from the para-hydrogen deriving protons to non-hydrogen non-zero nuclear spin (i.e. S≠0) nuclei in the hydrogenated compound, e.g. ^{13}C or ^{15}N nuclei. In this way, such non-zero spin nuclei may be given a nuclear spin polarization (hyperpolarization) equivalent to that

achieved in a kiloTesla or higher magnetic field. The nuclear magnetic resonance signal emitted by such hyperpolarized nuclei may be used for magnetic resonance imaging in much the same way or has been done with hyperpolarized ^3He-MRI. A similar nuclear spin hyperpolarization may likewise be achieved by hydrogenation with deuterium, more particularly with o-deuterium or with hydrogen ($^1H_2$)/deuterium ($^2H_2$) mixtures, particularly deuterium or hydrogen/deuterium mixtures in which the p/o ratio for hydrogen and the o/p ratio for deuterium are higher than the equilibrium values (1:3 and 2:1) at ambient temperature, e.g. having ratios corresponding to the equilibrium values at temperatures below 80K, more particularly temperatures below 40K, especially between liquid helium (4K) temperatures and 30K, more especially at temperatures between the melting points of the hydrogen and/or deuterium and 25K.

The hydrogenation and/or deuteration, e.g. of an unsaturated bond in a substrate molecule whereby to introduce a ^1H or ^2H atom bound to each of the atoms linked by the unsaturated bond, serves to introduce a hydrogen/deuterium spin and spin phase distribution into the hydrogenated substrate molecule which is other than the equilibrium distribution at ambient temperature. Where the substrate molecule contains non-zero nuclear spin nuclei (in natural or above natural isotopic abundances), particularly where these non-zero spin ($S\neq0$) nuclei are close in the molecular structure of the hydrogenated substrate to the ^1H or ^2H atoms introduced by the hydrogenation, the introduction ^1H or ^2H atoms can induce a nuclear spin and spin phase distribution in the $S\neq0$ nuclei which is other than the equilibrium distribution at ambient temperature. These non-equilibrium nuclear spin distributions for the introduced protons/deuterons and for the $S\neq0$ nuclei in the hydrogenated substrate may be harnessed to provide

signal enhancement in magnetic resonance imaging (MRI) techniques, including *in vivo* MRI.

The term "hyperpolarization" is used herein to denote a nuclear spin population distribution for a non-zero nuclear spin imaging nucleus in a hydrogenated substrate which is other than the equilibrium population distribution at ambient to physiological (e.g. 25-40°C) temperatures, more particularly for non-zero nuclear spin imaging nuclei in a hydrogenated substrate a distribution in which the population difference between ground and excited nuclear spin states is greater than the equilibrium population difference.

By "imaging nuclei" is meant the nuclei in the hydrogenated substrate responsible for the MR signal used in MRI to generate images. Thus, for example, the imaging nucleus might be a ^{13}C or ^{15}N nucleus, generally up to 4 bonds away from a ^{1}H or ^{2}H nucleus introduced by hydrogenation of the substrate, or it may be a ^{1}H or a ^{2}H nucleus introduced by hydrogenation of a non-symmetric unsaturated substrate. (Since the substrate is unsymmetrical the resonance frequencies of the two introduced hydrogens will not be the same).

While PCT/GB98/03399 does describe means by which para-hydrogen hydrogenation may be effected, we have now found that hydrogenation to harness for MRI the p-H_2 and/or o-D_2 induced hyperpolarization, the hydrogenation reaction is particularly favourably performed by mixing gaseous para-hydrogen and/or ortho-deuterium enriched hydrogen (i.e. where the p:o ratio of $^{1}H_2$ is greater than 1:3, particularly greater than 3:7, more particularly greater than 1:1 and/or the o:p ratio of $^{2}H_2$ is greater than 3:2, particularly greater than 3:1, more particularly greater than 4:1) with a spray of a solution of the unsaturated compound and a hydrogenation catalyst.

Viewed from one aspect the invention thus provides a process for the preparation of an MR contrast agent,

said process comprising:

i) obtaining a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of said substrate compound;

ii) introducing said solution in droplet form into a chamber containing hydrogen gas (H_2) enriched in para-hydrogen ($p\text{-}^1H_2$) and/or ortho-deuterium ($o\text{-}^2H_2$) whereby to hydrogenate said substrate to form a hydrogenated imaging agent;

iii) optionally subjecting said hydrogenated imaging agent to a magnetic field having a field strength below earth's ambient field strength;

iv) optionally dissolving said imaging agent in an aqueous medium;

v) optionally separating said catalyst from the solution of said imaging agent in said aqueous medium;

vi) optionally separating said solvents from the solution of said imaging agent in said aqueous medium; and

vii) optionally freezing the solution of said imaging agent in said aqueous medium.

In optional step (iii) of the process of the invention, the hydrogenated imaging agent is subjected to a low magnetic field treatment. This step is desirably effected unless the MR imaging procedure is to use as imaging nuclei deuterons introduced by deuteration with ortho-D_2 (i.e. gas comprising D_2 where the $o\text{-}D_2$:$p\text{-}D_2$ ratio is greater than 2:1). The low field treatment may be effected at any stage following onset of hydrogenation, and indeed the process of the invention may be performed in its entirety in a low field; however it is desirable that the low field treatment occur before water addition (optional step (iv)) in order both to avoid enhancement by the low field of hyperpolarization loss induced by paramagnetic materials which may be present (e.g. as minor

impurities, or as dissolved oxygen) in the water and because protons in the water would themselves have a relaxing effect. Accordingly it is preferred that the low field treatment be of the hydrogenation reaction medium (e.g. by placing at least part of the chamber in a low field) and/or of the reaction medium drawn out from the chamber. Low field treatment (e.g. at fields below 50 μT, preferably less than 1 μT) may be achieved by magnetic shielding using commercially available materials, e.g. μ-metal, and may be particularly suitably achieved by disposing some or all of the apparatus used for the process of the invention in a magnetically shielded container such as is described in WO99/17304.

The low magnetic field treatment may alternatively be effected by passage through a twin μ-metal layer tube, capable of giving a field of less than 1 μT, more preferably less than 0.5 μT inside.

Most imaging agents will require this low magnetic field treatment for one of two reasons, first that this promotes polarization transfer from the introduced ^{1}H or ^{2}H nuclei to the imaging nuclei (e.g. ^{13}C, ^{15}N, etc.) and secondly as the treatment transforms the line-shape of the MR signal from an anti-phase multiplet with zero integral to a multiplet with a net signal which is good for imaging.

The hydrogenatable substrate used may be a material such as is discussed in PCT/GB98/03399 as a para-hydrogenation substrate. For *in vivo* imaging studies, the substrate is preferably a material which is physiologically tolerable both in hydrogenated and unhydrogenated forms. For ^{2}D-MR studies, the substrate is desirably non-symmetrical about the unsaturated bond which is hydrogenated, especially preferably non-symmetrical within 4 bonds of the unsaturated bond (e.g. $H_5C_2OOCCH_2CH{=}CH{-}CH_3$ would be considered to be unsymmetrical within 2 bonds of the ethylenic C:C double

bond).

For *in vitro* or *in vivo* MR studies of biological or quasi-biological processes or synthetic polymer (e.g. peptide, poly-nucleic acid etc.) syntheses, the substrate is preferably hydrogenatable to form a molecule participating in such reactions, e.g. an amino acid, a nucleic acid, a receptor-binding molecule, etc., either a natural such molecule or an analog.

The solvent used in step (i) of the process of the invention may be any convenient material which serves as a solvent for the substrate and the hydrogenation catalyst. Preferably however it is a volatile organic solvent (e.g. acetone) especially one which is water miscible, especially preferably it is not water (i.e. not ^1H_2O) and especially preferably it is perdeuterated (e.g. $C^2H_3OC^2H_3$ or d_6-acetone). Where the imaging agent is for use in *in vivo* MR investigations, the solvent is preferably physiologically tolerable. Solvent removal (optional process step (vi)) is preferably effected by vacuum, e.g. by spray-flash distillation. Other rapid solvent removal techniques, e.g. affinity techniques, may however be used.

The solvent is preferably used at or near the minimum quantities required to maintain substrate, catalyst and imaging agent in solution during the hydrogenation reaction.

The hydrogenation catalyst is preferably a catalyst as discussed in PCT/GB98/03399, e.g. a metal complex, in particular a rhodium complex.

The enriched hydrogen, which may be pure $^1H_2$ or $^2H_2$, or a mixture of $^1H_2$ and $^2H_2$ (perhaps containing some HD), optionally containing other gases although preferably free from oxygen or other reactive or paramagnetic gases, may be prepared by cooling hydrogen (i.e. $^1H_2$, $^2H_2$ etc.), preferably to a temperature below 80K, more preferably to a temperature below 30K, still more preferably to a temperature below 22K, and allowing the

nuclear spin states to equilibrate, optionally in the presence of a solid phase equilibration promoter, e.g. Fe_3O_4, Fe_2O_3, activated charcoal, etc. The enriched hydrogen is then preferably removed from the equilibrator and optionally stored before use, preferably at a reduced temperature, e.g. 20-80K. The preparation and storage of enriched hydrogen is described in PCT/GB98/03399 the contents of which are incorporated herein by reference.

For the hydrogenation reaction, enriched hydrogen is filled into a reaction chamber optionally under pressure, e.g. 50 to 100 bar, and the catalyst and substrate solution is introduced in droplet form, e.g. by spraying or atomizing, into this reactor. If desired, the solution may be produced by mixing separate solutions of catalyst and of substrate. To ensure proper mixing, a distributor or a plurality of spray nozzles may be used and the chamber contents may be mixed, e.g. by a mechanical stirrer or by appropriately shaping the chamber walls where there is a flow of reaction mixture in the chamber. The process may be performed continuously with a flow reactor, e.g. a loop or tube reactor, or alternatively it may be a batch-wise process. Preferably however there will be a continuous or pulsed flow of enriched hydrogen and solution spray into the reactor, a continuous or batch-wise removal of liquid solution from the base of the reactor, and a continuous or batch-wise venting of unreacted gas from the reactor. The enriched hydrogen and solution passing into the reactor are preferably temperature-controlled to ensure the gas-droplet phase in the reactor is at the desired temperature. This can be achieved by providing input lines with temperature sensors and heating or cooling jackets.

Following hydrogenation and any optional, although generally preferred low magnetic field treatment, the imaging agent is preferably mixed with water. The water

used is preferably sterile and also preferably essentially free of paramagnetic contaminants. The resultant aqueous solution is then preferably treated to remove the hydrogenation catalyst, e.g. by passage through an ion exchange column, preferably one free of paramagnetic contaminants. The water may be temperature-controlled as may be a mixing chamber where water and imaging agent solutions are mixed so as to ensure the aqueous solution enters the ion exchange column at the appropriate temperature. Strongly acidic, sodium ion charged ion exchange resins such as DOWEX 1x2-400 (Dow Chemicals) and Amberlite IR-120 (both available from Aldrich Chemicals) resins may conveniently be used for the removal of typical metal complex hydrogenation catalysts. For fast ion exchange, the resin is preferably cross-linked to only a low degree, e.g. a 2% divinyl benzene cross-linked sulphonated, sodium ion loaded polystyrene resin.

Removal of the non-aqueous solvent may then conveniently be effected by spray flash distillation - e.g. by spraying the aqueous solution into a chamber, applying a vacuum, and driving the organic solvent free aqueous solution from the chamber using an inert, preferably non-paramagnetic gas, e.g. nitrogen. Indeed in general the flow of liquid components through the hydrogenation apparatus will preferably be effected using applied nitrogen pressure, e.g. 2 to 10 bar.

The resulting aqueous imaging agent solution may be frozen and stored or alternatively may be used directly in an MR imaging or spectroscopy procedure, optionally after dilution or addition of further solution components, e.g. pH modifiers, complexing agents, etc. Such direct use may for example involve continuous infusion or alternatively injection or infusion of one or more dose units. Bolus injection is particularly interesting.

The whole process from beginning of hydrogenation

to end of solvent removal may conveniently be effected in less than 100 seconds, indeed it is feasible to produce dosage units in as little as 10 to 20 seconds, which is substantially less than T_1 for the imaging nuclei in many of the imaging agents in the contrast media so produced.

Desirably, the surfaces contacted by the imaging agent during the process of the invention are substantially free of paramagnetic materials, e.g. made of glasses as used for hyperpolarized ^3He containment as discussed in WO99/17304 or gold or a deuterated polymer. Surfaces contacting the non-aqueous solvent (e.g. acetone) should be acetone resistant and valves may be magnetically controlled with solvent resistant Teflon or silicon parts.

The process of the invention may conveniently be automated and computer-controlled.

Viewed from a further aspect the invention provides a hydrogenation apparatus comprising a hydrogenation chamber having a liquid outlet into a conduit leading to a liquid droplet generator inlet (e.g. a spray nozzle) to a solvent removal chamber,

said hydrogenation chamber having a hydrogen inlet and a solution inlet provided with a further liquid droplet generator;

said conduit including a catalyst removal chamber (e.g. containing an ion exchange resin) between said hydrogenation chamber and said solvent removal chamber and being provided, preferably between said hydrogenation chamber and said catalyst removal chamber, with a liquid inlet (e.g. a water inlet); said solvent removal chamber being provided with a gas outlet (e.g. attached to a vacuum source) and with a liquid outlet (e.g. to an optional formulation chamber and thence to administration means or to a dose unit receiver (e.g. a syringe)), and

said hydrogenation apparatus being further provided

with magnetic shielding such that the magnetic field within at least part of said hydrogenation chamber and/or within at least part of said conduit (preferably the part upstream of the liquid (water) inlet) is <50 μT, more preferably <1 μT.

The apparatus of the invention is preferably also provided with reservoirs and mixing chambers appropriate for the materials being fed in, e.g. an enriched hydrogen reservoir, a water reservoir, a reservoir for solutions of hydrogenation catalyst and/or hydrogenatable substrate, reservoirs for further contrast medium components, a mixing chamber for mixing solutions of catalyst and substrate, a mixing chamber for mixing water with the solution exiting the hydrogenation chamber, etc. Likewise the hydrogenation chamber is preferably provided with a vent for removing hydrogen and various of the chambers and reservoirs are preferably provided with nitrogen sources and nitrogen inlets to drive their contents into or through the apparatus. Particularly preferably, the apparatus also includes an enriched hydrogen generator, valves, valve actuators and a computer control for controlling apparatus operation.

The magnetic shielding is preferably removable so that it can be removed if ^{2}H-imaging is desired.

The chambers and conduits of the apparatus of the invention are preferably sealable to prevent ingress of air; moreover, the apparatus is preferably provided with valves and ports arrangeable to permit degassing, in particular to remove surface adsorbed oxygen.

The water input to the apparatus of the invention is preferably deoxygenated, e.g. by treatment with nitrogen.

The "chambers" in the apparatus of the invention may have internal cross-sectional areas which are larger than the internal cross-sectional areas of the chamber inlets or outlets (in the flow direction); alternatively

the cross-sectional areas in the flow direction may be substantially invariant, i.e. a tube may function as inlet-chamber-outlet.

The use of heterogeneously catalysed "spray-hydrogenation" in the preparation of MR contrast agents is new. Likewise such hydrogenation is new in the preparation of amino acids and pharmaceuticals. The procedure is rapid and efficient and this forms a further aspect of the invention. Viewed from this aspect the invention provides a process for the preparation of an amino acid, a pharmaceutical or an *in vivo* diagnostic agent, characterised in that said process comprises a hydrogenation step in which a solution of a substrate and a hydrogenation catalyst is sprayed into a hydrogen-containing chamber.

Where the hydrogenation is effected using a gas in which the $^2H:^1H$ ratio is in excess of 9:1, using $p\text{-}D_2$, the use of heterogenous catalysis is also contemplated - in this event catalyst removal may involve filtering or other particulate removal techniques.

The contents of all publications referred to herein are hereby incorporated by reference.

Embodiments of the process and apparatus of the invention will now be described with reference to the following non-limiting Example and to the accompanying drawings, in which:

Figure 1 is a schematic view of one apparatus according to the invention;

Figure 2 is a schematic view of part of the apparatus of Figure 1; and

Figure 3 is a schematic view of a further part of the apparatus of Figure 1.

Referring to Figure 1, hydrogen ($^1H_2$) from cylinder 1 is fed via tube 2 to a $p\text{-}^1H_2$ generator and thence into hydrogenation chamber 3. A hydrogenation catalyst solution from reservoir 4 and a hydrogenatable substrate solution from reservoir 5 are fed via lines 6 and 7 to a

spray nozzle in chamber 3. The liquid settling in chamber 3 passes via conduit 8 through a twin μ-metal layered tube 9, a magnetic shield having an internal field of less than 0.5 μT, into an ion exchange column 10 and thence to a spray nozzle in the solvent removal chamber 11. Before the liquid enters the ion exchange column but after it exits the magnetic shielding, water from reservoir 12 is added via tube 13. Solvent removal chamber 11 is connected via tube 14 to a vacuum pump 15 which serves to remove non-aqueous solvent, e.g. acetone. The liquid remaining in chamber 11 is removed via exit duct 16.

Referring to Figure 2, it can be seen that nitrogen (at 3 bar) is used to drive catalyst and substrate solutions from reservoirs 4 and 5 to a water-jacketed mixing chamber 17 and thence to the spray nozzle 18 in hydrogenation chamber 3 which is provided with a valved hydrogen vent 19. Nitrogen may be used to drive the liquid collecting in the hydrogenation chamber through the magnetic shielding 9 to mix with nitrogen driven water from reservoir 12. Turning to Figure 3, the solution/water mixture passes into water-jacketed mixing chamber 20 and thence through a 2 to 4-cm long ion exchange column 10 containing 400 mesh sulphonated polystyrene/2% DVB and on to spray nozzle 21 in solvent removal chamber 11. To ensure complete non-aqueous solvent removal, the chamber 11 is buffered with a cooling trap (not shown) followed by a second volume before the vacuum pump - this relieves the very sudden load otherwise put on the pump. After release from the chamber 11, the aqueous "contrast medium" is ready for use; alternatively its pH may be buffered and its ion profile adjusted (e.g. to add plasma cations).

There are two preferred modes of operation; in one the apparatus is used to fill a syringe which is removed and the contrast medium is injected; in the second, the apparatus delivers small doses of contrast medium

continuously to a catheter linked to the patient. The second mode allows for easier imaging since the operator can adjust the MR imager to obtain a satisfactory image.

EXAMPLE 1

A solution of (bicyclo[2.2.1]hepta-2,5-diene)-[1,4-bis(diphenylphosphino)butane]-rhodium(I) tetrafluoroborate (93.5mg) in argon-bubbled acetone (5ml) is charged in chamber A and a solution of 2-acetoxyacrylic acid (110mg, 0.85mmol) in argon-bubbled acetone (5ml) in chamber B. Chamber E is filled with distilled, argon-bubbled water. Ion exchange resin of type sulphonated polystyrene, 2% cross-linked, swelled with water and charged with sodium ions is loaded in the ion exchange column. Water at 42°C is circulated through the jackets in the set-up. The experiment is started by running a computer program that controls the valves according to scheme 1 as shown in Table 1 below. The program is written in LabView. After the program is finished the sample of aqueous hyperpolarized O-acetyl lactic acid is removed at the bottom of chamber G by a syringe.

A $3m^3/hr$ 2-stage diaphragm pump is used to provide the vacuum and 3 bar of nitrogen is used as the driving pressure. The spray nozzles are ordinary commercial oil-burner nozzles, the one in chamber D is specified as 1.5 US gallon/hr with a 60° cone angle, the one in chamber G is 1.0 US gallon/hr with a 80° cone angle. The magnetic valves are 8W, 24V DC with gaskets of EPDM.

The magnetic screen is made from two concentric tubes of μ-metal

Table 1

Valve No. / Time/s	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Comment
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Start
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Pressurise
	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	Fill water loop until overflow is detected
	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	Fill catalyst and substrate loops until overflow is detected
0.2	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	Add catalyst and substrate to C intermittently
0.2	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	Loop 15 times
10	0	0	1	1	0	1	1	0	0	0	0	0	0	0	1	0	0	0	Allow pressure to build up in C, evacuate D
10	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	Fill D with para-hydrogen, evacuate-G
12	0	0	1	0	0	1	0	1	0	0	0	0	1	0	0	1	0	0	Spray mixture into D and dry overflow sensors
5	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	Suck reaction mixture to F
8	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	0	0	Add water and mix
20	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1	0	0	Spray into G
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	Increase pressure in G
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	Equilibrate pressure in G with atmosphere
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Finished

Claims

1. A process for the preparation of an MR contrast agent, said process comprising:

i) obtaining a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of said substrate compound;

ii) introducing said solution in droplet form into a chamber containing hydrogen gas (H_2) enriched in para-hydrogen (p-$^1H_2$) and/or ortho-deuterium (o-$^2H_2$) whereby to hydrogenate said substrate to form a hydrogenated imaging agent;

iii) optionally subjecting said hydrogenated imaging agent to a magnetic field having a field strength below earth's ambient field strength;

iv) optionally dissolving said imaging agent in an aqueous medium;

v) optionally separating said catalyst from the solution of said imaging agent in said aqueous medium;

vi) optionally separating said solvent from the solution of said imaging agent in said aqueous medium; and

vii) optionally freezing the solution of said imaging agent in said aqueous medium.

2. A hydrogenation apparatus comprising a hydrogenation chamber having a liquid outlet into a conduit leading to a liquid droplet generator inlet to a solvent removal chamber,

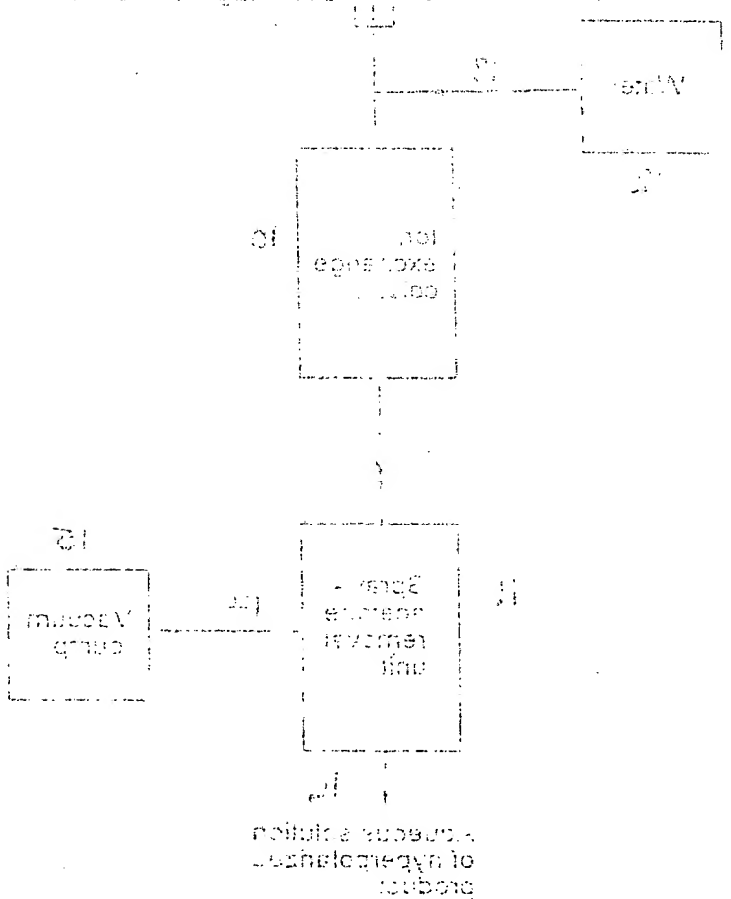
said hydrogenation chamber having a hydrogen inlet and a solution inlet provided with a further liquid droplet generator,

said conduit including a catalyst removal chamber between said hydrogenation chamber and said solvent removal chamber and being provided, preferably between said hydrogenation chamber and said catalyst removal chamber, with a liquid inlet, said solvent removal

chamber being provided with a gas outlet and with a liquid outlet, and

said hydrogenation apparatus being further provided with magnetic shielding such that the magnetic field within at least part of said hydrogenation chamber and/or within at least part of said conduit (preferably the part upstream of the liquid (water) inlet) is <50 μT, more preferably <1 μT.

3. A process for the preparation of an amino acid, a pharmaceutical or an *in vivo* diagnostic agent, characterised in that said process comprises a hydrogenation step in which a solution of a substrate and a hydrogenation catalyst is sprayed into a hydrogen-containing chamber.



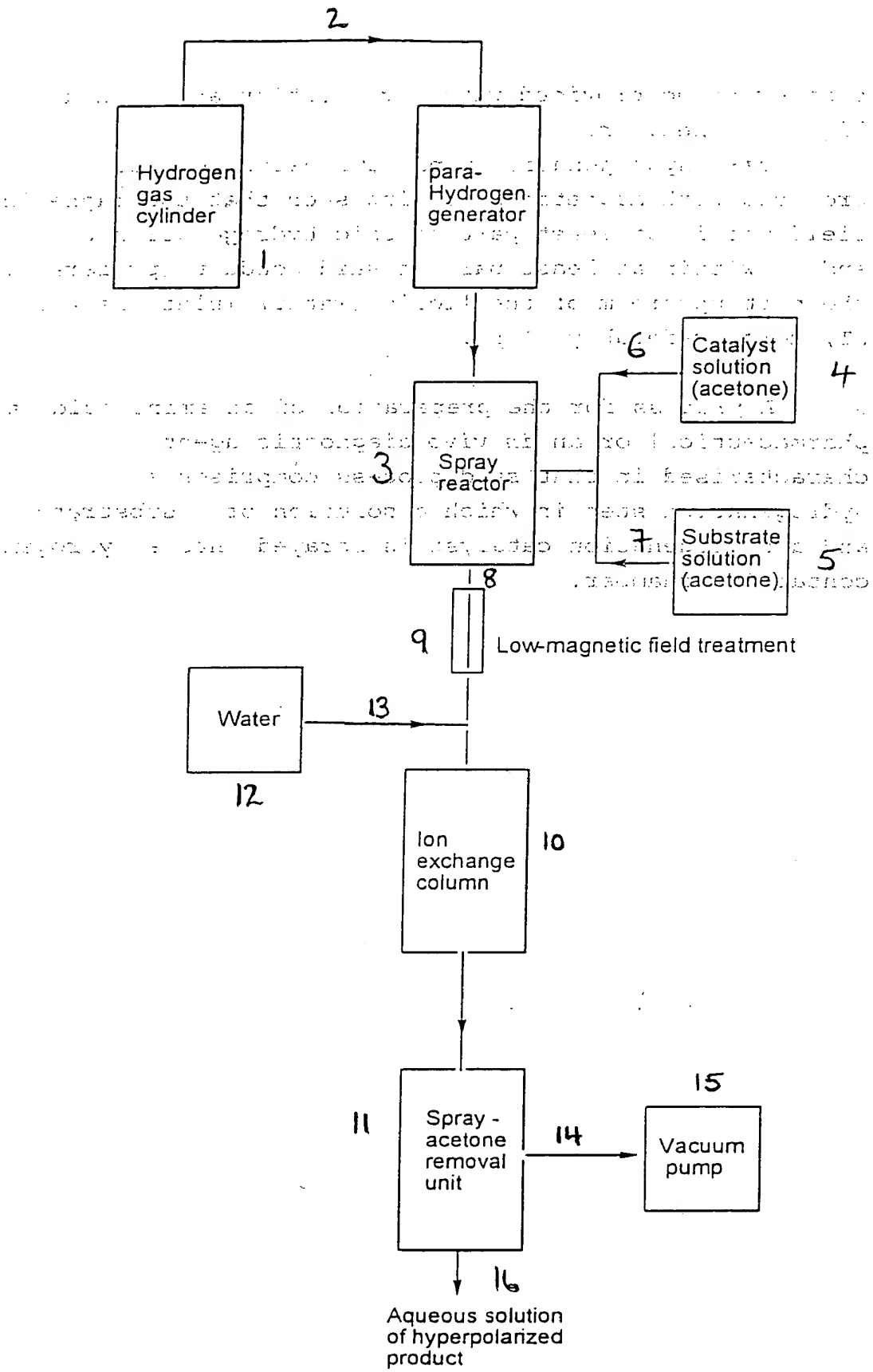

2
Hydrogen gas cylinder
1
para-Hydrogen generator
6
Catalyst solution (acetone)
4
3
Spray reactor
7
Substrate solution (acetone)
5
8
9
Low-magnetic field treatment
Water
13
12
Ion exchange column
10
11
Spray - acetone removal unit
14
15
Vacuum pump
16
Aqueous solution of hyperpolarized product

Fig 1

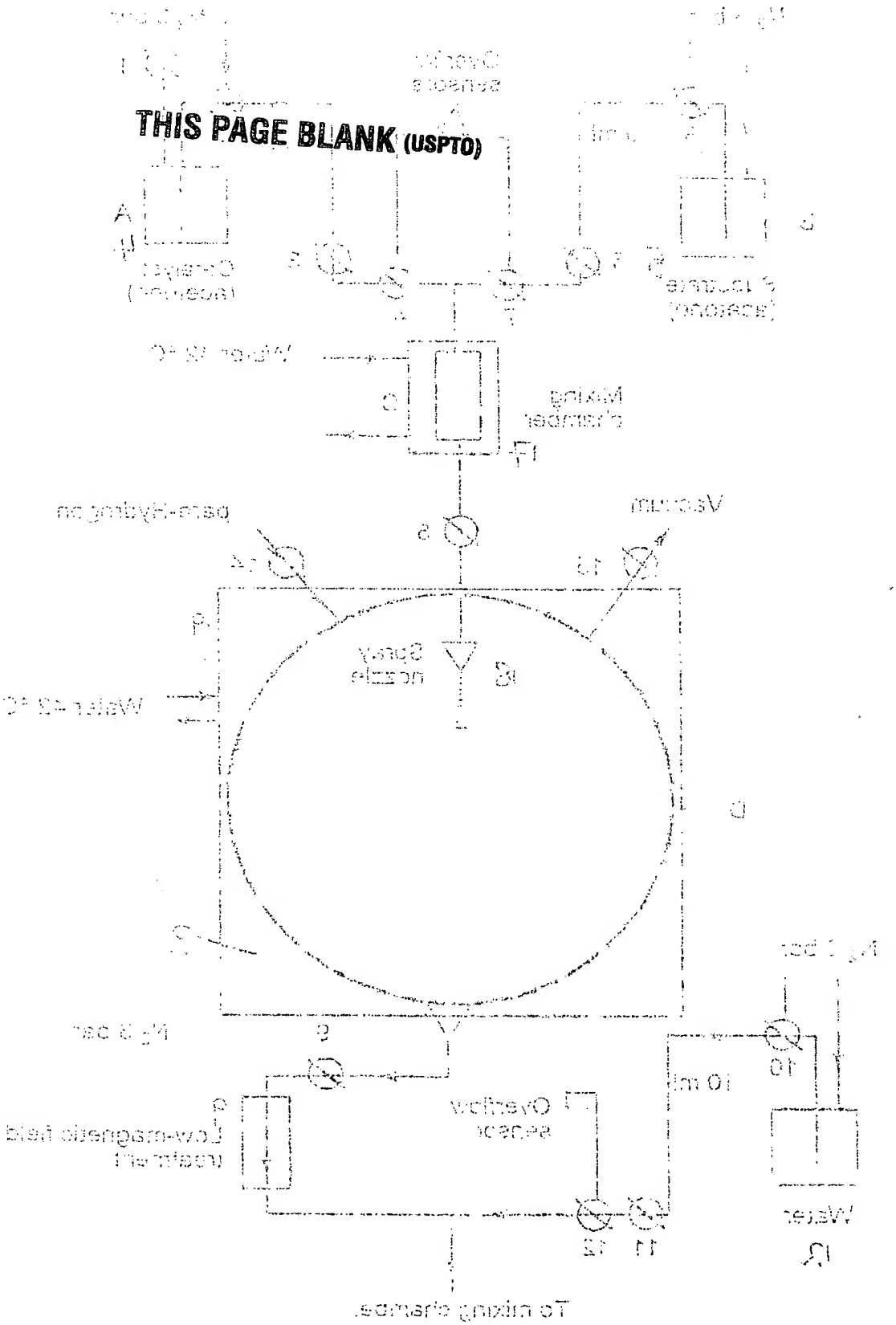


Fig. 2

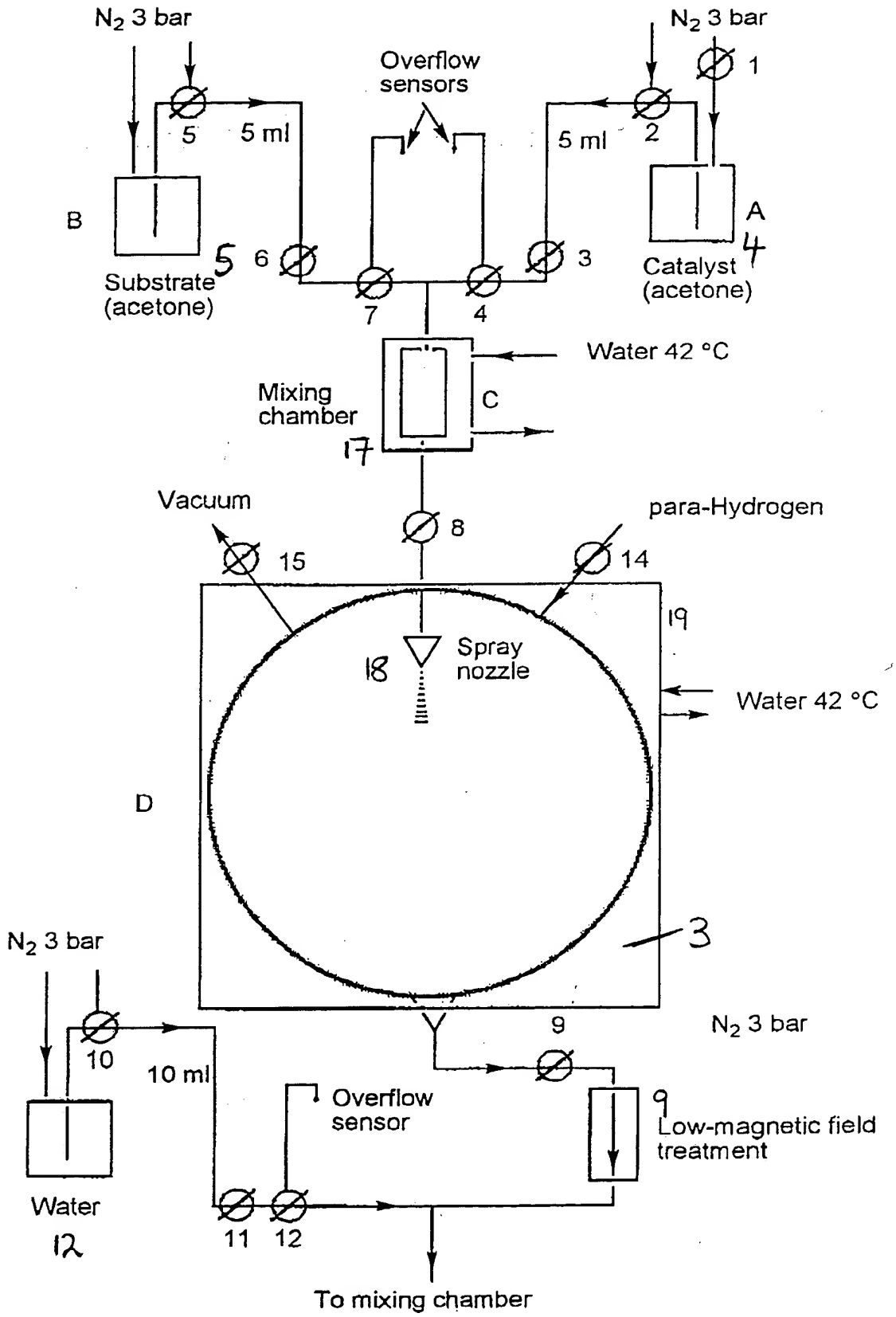
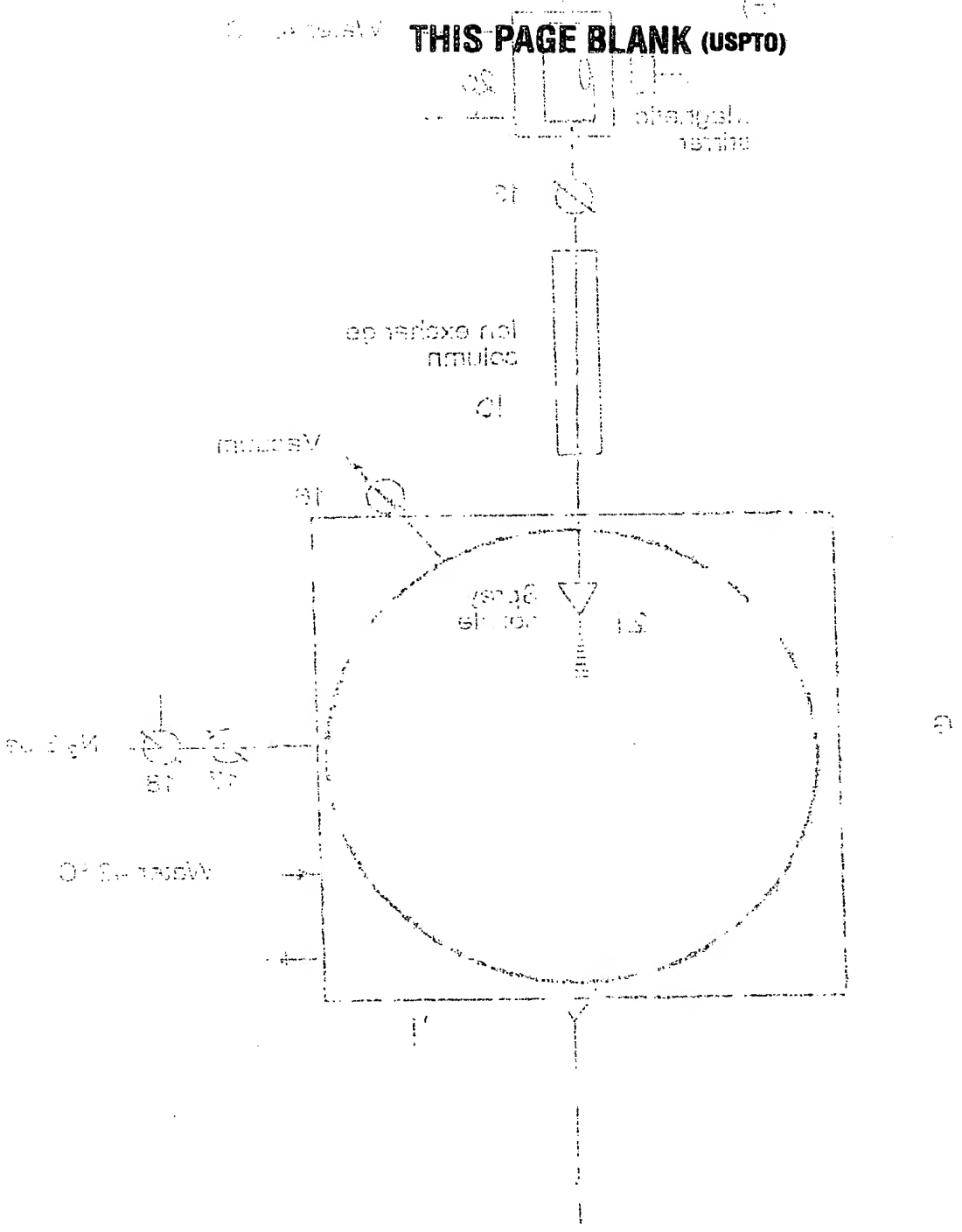

N_2 3 bar
N_2 3 bar
Overflow sensors
1
5
5 ml
5 ml
2
B
A
4
Substrate (acetone)
5
6
3
Catalyst (acetone)
7
4
Water 42 °C
Mixing chamber
C
17
Vacuum
8
para-Hydrogen
15
14
19
18
Spray nozzle
Water 42 °C
D
3
N_2 3 bar
9
N_2 3 bar
10
10 ml
Overflow sensor
9
Low-magnetic field treatment
Water
12
11
12
To mixing chamber

Fig 2



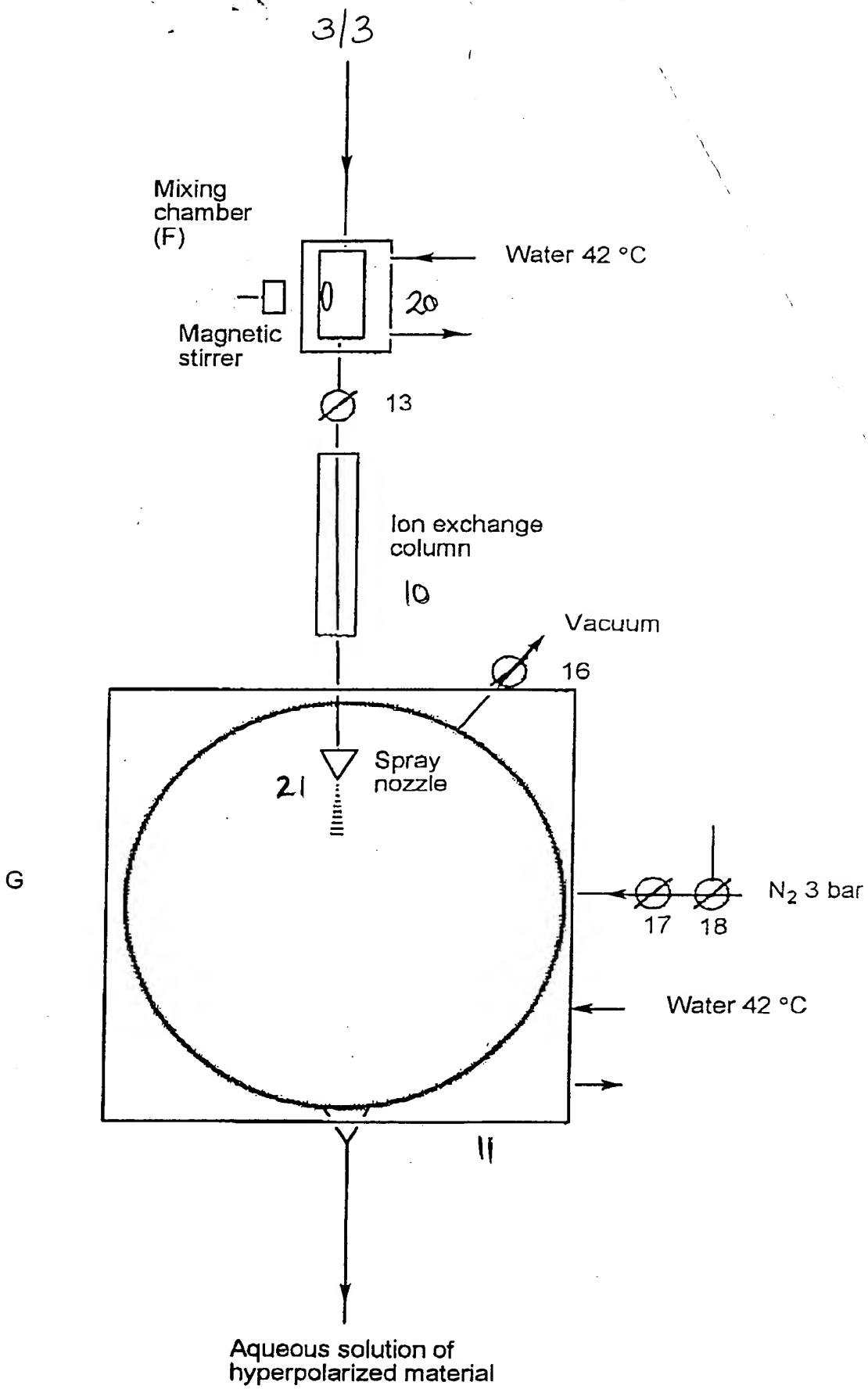

Mixing chamber (F)
Water 42 °C
Magnetic stirrer
20
13
Ion exchange column
10
Vacuum
16
Spray nozzle
21
G
N_2 3 bar
17
18
Water 42 °C
11
Aqueous solution of hyperpolarized material

Fig 3